PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No.	10/501,887
Filing Date	April 6, 2005
Applicants	Velebny et al.
Title	**PREPARATION FOR WOUND HEALING AND PREVENTION OF BANDAGE ADHESION TO THE WOUND**
Art Unit	1614
Examiner	Finn
Confirmation No.	6569
Attorney Docket No.	074047.2

December 16, 2009

DECLARATION PURSUANT TO 37 C.F.R. §1.132

DECLARATION 3

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

1. This Declaration is being made in order to distinguish the claimed invention from the teachings of the references Drizen et al. (US 20020037319) and Cantor et al. (US 20030054025) cited in the claim rejections according to § 103.

2. The graph (Enclosure I) shows the relation between the HA molecular weight and the wound healing. Specifically, the graph shows the percentage of the healed area of the wound 216 hours after the wound is formed (100 % is a completely healed wound). Untreated wounds heal after such period of time just by 40 to 45 %. It is clear why we chose the lowest limit of the HA molecular weight of 200,000 - in case the molecular weight is lower than 200,000, the healing speed is basically the same as that of the control (which was not treated with the preparation according to the invention). Further, the graph shows that the hyaluronan having the molecular weight higher than about 800,000 to 900,000 has practically the same effect on the healing speed. When reducing the molecular weight of the hyaluronan, a slow decrease appears until the values of about 200,000. We have not measured the healing speed of hyaluronan having the molecular weight higher that 1,500,000 in the experiment from which the graph is obtained but we know, based on the pre-clinical and clinical tests that hyaluronan having the molecular weight up to 2,500,000 acts practically the same as the hyaluronan having the molecular weight of about 1,500,000, which is the final point in the graph. Therefore, we have determined that HA having a molecular weight range from approximately 850,000 to 2,500,000 is similar in the ability to promote wound healing.

3. No one produces or protects a preparation based on a complex of iodine and any other substance, i.e. not only hyaluronan. A combination of hyaluronan and PVP-iodide, i.e. a form of iodine, was patented, which in the 50's replaced the complex of iodine with iodide and which itself has much better characteristics than the complex of iodine and iodide (see Enclosures VI and IX, of record, submitted July 25, 2008). We believe it is a clear proof of the fact that a person skilled in the field of using iodine in preparations for wound healing would realize the limitations of the complex of iodine with iodide and thus would choose PVP-iodide rather than the complex of iodine with iodide.

4. It would not make sense to go back to the once obsolete disinfectant which is known to have a number of negative factors which the complex of iodine with iodide has to the wound healing (it does not support the healing, it is three times more toxic than PVP-iodide, painful when applied, skin coloring effect, iodine volatility in the preparation and thus a difficult storability of the preparation etc.). Also, there were much

more modern disinfectants at the time of the conception of the invention. Therefore, there is a total lack of a rational reason to go back to a disinfectant which has been out of use for over 50 years if a new, unpublished property of the complex of iodine with potassium iodide were not discovered. This means that the reestablishment (re-use) of the complex of iodine and iodide must have been preceded by a research and development activity including an inventive step. Otherwise it is really beyond reason why a person skilled in the art, knowing the negative characteristics of the complex, having other and so far unpatentable combinations of disinfectants with hyaluronan, would return to such a disinfectant.

5. The decrease of the healing time which is caused by the combination of hyaluronan and iodine-iodide complex, is basically due to the following factors which had not been published until the filing of the patent application (therefore, an inventive step must have been applied):

a) hyaluronan in the combination with iodine-iodide complex activates keratinocytes to produce cytokines; the cytokines activate the chemoattraction of the immune cells which speed up the wound healing. Neither the complex itself, nor the hyaluronan itself is able to do that - the combination of both is required. This is stated in our patent application in par. 0026. The explanation of this lies in the ability of hyaluronan to interact with the cells by means of the CD44 receptor which enables the complex to be transported to the cell if it is in combination with hyaluronan. The complex itself (without hyaluronan) is unable to get into the cell.

b) We have proved that the wound healing is positively influenced just by hyaluronan having such a molecular weight which is able to retain a certain amount of water. On the wound, a relatively rapid decomposition of hyaluronan into fragments occurs, said fragments not being able to retain a sufficient amount of water. According to our research, the healing effect of hyaluronan is caused by the fact that hyaluronan is able to bind a relatively high amount of water which it takes from the underlay of the wound where the healing active substances (growth and other regulation factors) are produced by other cells. This results in bringing a greater amount of these factors to the wound than in the case when the wound is being healed in an uninfluenced manner, just by a simple diffusion of said factors from the underlay of the wound. Enclosure II (also submitted as Enclosure XI of record, submitted July 25, 2008) shows the decrease of the molecular weight of hyaluronan which was applied to the wound in absence and in presence of the iodine-iodide complex. This complex stabilizes hayluronan within the wound. Our statement is further supported by the lack of success of the company LAM Pharma with the preparation I.P.M. Wound Gel on the market. It was a pure hyaluronan without any agent which would retard its decomposition. This preparation was withdrawn from the market as it was ineffective. According to our measurements, the reason was just the rapid decomposition of hyaluronan, and therefore, the loss of its ability to bind water.

c) Another important factor was to protect the underlay itself of the wound and the surrounding tissues from the devastation by tissue proteases. If they are not protected, the wounds heal poorly, especially the chronic wounds, which are very nicely healed by the preparation according to our invention (hereinafter

called "Hyiodine"). We have clearly proved that the combination of hyaluronan with iodine-iodide complex inhibits two main classes of proteases which act in tissues: serine proteases (the representative being trypsin) and metaloproteases (the representative being collagenase). An important factor for the wound healing is protection of wound bottom layer and surrounding tissue from devastation by tissue proteases. It is very well known that one of the reasons that causes difficult wound healing of chronic wounds is their devastation by proteases. The most important of them are tissue metalloproteinases (matrix metalloproteinases – MMP). A certain role is also played by serine proteinases (mainly from blood cells). Therefore we studied the influence of hyaluronan with and without iodine complex on the activity of collagenase II (metalloproteinase) (see Enclosure III, the upper graph showing the inhibitory effect of KI_3 on the activity of type II collagenase) and on the activity of trypsin (serine proteinase) (see Enclosure III, the lower graph showing the inhibitory effect of KI_3 on the activity of trypsin). Both enzyme activities were inhibited by the hyaluronan – iodine complex in contrast to hyaluronan without complex. The inhibition effect of collagenase II was found very strong, the inhibition of trypsin was weaker but significant. These results demonstrate the unexpected role of hyaluronan – iodine complex, namely its ability to inhibit MMP and also serine proteinases and thus protect the wound surrounding tissue from the destruction and thereby also support and accelerate wound healing which is in a very good agreement with clinical findings; Hyiodine is able to heal various wounds very well.

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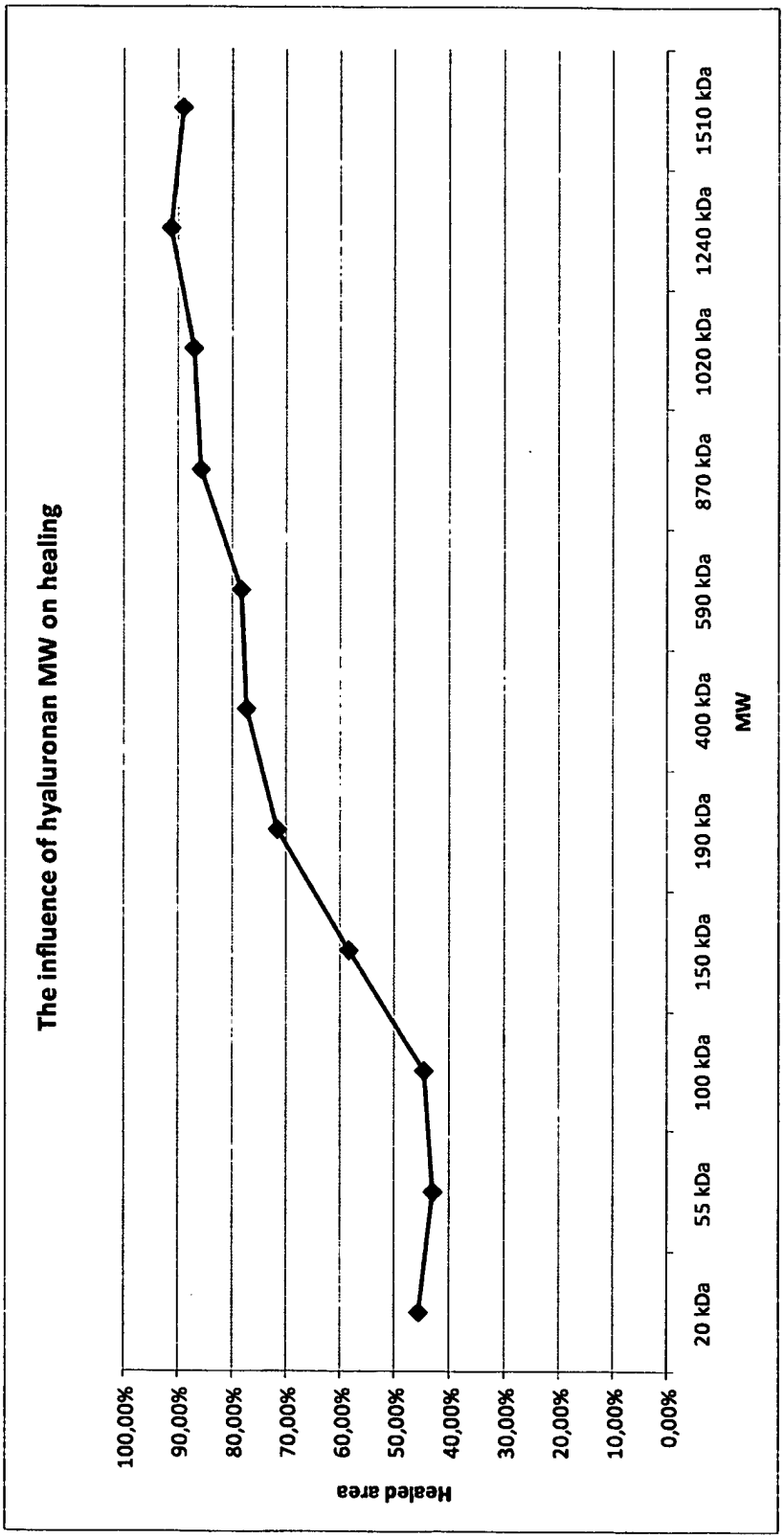
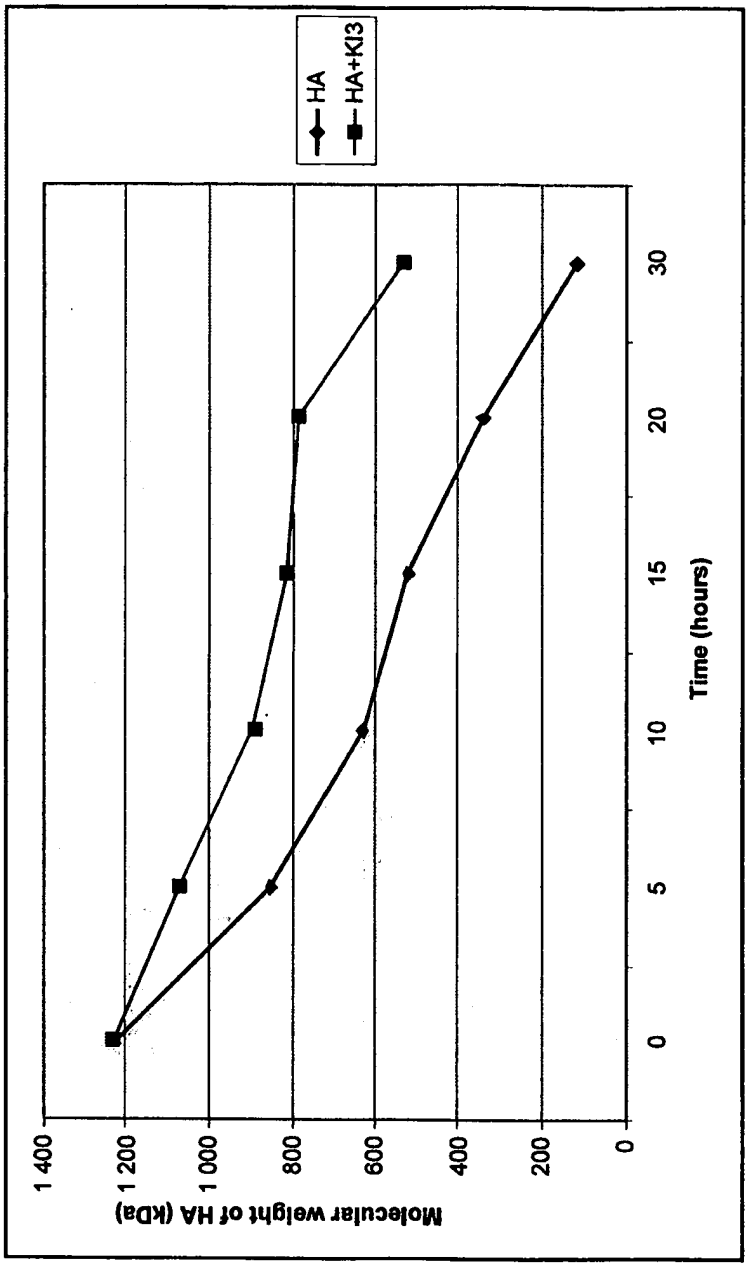
ENCLOSURE I


The influence of hyaluronan MW on healing
Healed area
100,00%
90,00%
80,00%
70,00%
60,00%
50,00%
40,00%
30,00%
20,00%
10,00%
0,00%
20 kDa
55 kDa
100 kDa
150 kDa
190 kDa
400 kDa
590 kDa
870 kDa
1020 kDa
1240 kDa
1510 kDa
MW

ENCLOSURE II



HA = hyaluronic acid;
HA+KI3 = the mixture of hyaluronic acid with potassium triiodide complex

ENCLOSURE III